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Nocturnal Serum Growth Hormone Concentration is not Augmented by Short-Term Testosterone Infusion in Pubertal Boys

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ABSTRACT. Chronic exposure to testosterone (T) increases growth hormone (GH) secretion. To determine whether acute exposure to T would also enhance GH secretion, we infused saline, followed 1 wk later by T, for 18–24 h at one-third the adult male production rate in 12 pubertal boys and at the adult male production rate in eight additional pubertal boys. Blood was obtained every 20 min for GH and every 30 min for T from 2000–0800 h. Though infusion significantly increased serum T concentrations in all 20 boys, mean GH concentration, GH pulse frequency, and GH pulse amplitude did not increase compared to the saline infusion night. The secretory dynamics of GH as a function of 3-h time blocks from 2000–0800 h were also determined in the eight boys who received the higher dose of T. The profile for mean GH concentration, pulse frequency, pulse amplitude, and peak area were not affected by acute infusion of T at concentrations sufficient to alter LH secretion. This suggests that, at least in pubertal boys, one must be exposed to T for a period longer than 12–18 h to induce increased GH secretion. (*Pediatr Res* 26: 320–324, 1989)

Abbreviations

GH, growth hormone
T, testosterone
LH, luteinizing hormone
SmC, somatomedin C
CV, coefficients of variation

It has long been established that GH is secreted episodically throughout the day with significant augmentation during sleep in children and adults (1–5). Inasmuch as most of the GH is secreted during the nighttime hours, GH secretion rates calculated on the basis of 24-h sampling correlate well with those calculated on the basis of 12-h nighttime sampling (6, 7). Overall GH pulse frequency and/or amplitude are known to be acutely affected by fasting (8) and the sex steroid milieu (9–11).

In children, treatment with androgens or estrogens has resulted in increased GH release to pharmacologic stimuli (12–14). GH pulse amplitude but not frequency is increased by T treatment of at least 3 mo duration (10, 15). Therapy with T enanthate in boys with constitutional delay in growth and low GH secretion results in increased GH secretion as well as acceleration of growth velocity (10, 16, 17). It therefore appears that the growth acceleration during spontaneous puberty may be related to the effects of sex steroids upon GH secretion as well as direct effects of sex steroids on tissues.

We studied GH secretion before and during T infusion in 20 early to midpubertal boys to determine whether the acute elevation of T to concentrations known to alter LH secretion (18, 19), would also affect the neuroendocrine signals regulating GH secretion. Mean integrated GH concentrations were calculated from 12-h nocturnal serum samples obtained every 20 min during a saline infusion night and compared to the results obtained during a T infusion night. T was administered at one-third of the adult male blood production rate in 12 boys and at the adult male production rate in eight boys.

MATERIALS AND METHODS

Subjects. The clinical characteristics and diagnoses of the 20 boys studied are listed in Table 1. All boys (with the exception of patient 20) had delayed adolescent development and 17 of the 20 had ht less than the fifth percentile for age. When ht percentiles were corrected for bone age, no ht was more than 2 SD from the mean. SmC levels, bone age x-rays, and thyroid function tests had been determined within the 3 mo before the study. Thyroid function was normal in all boys. All boys had participated in studies of LH secretion in response to T infusion, and these results are reported elsewhere (18, 19). Peak GH concentrations in response to arginine (0.5 g/kg intravenous over 30 min), insulin (0.1 U/kg intravenous), after 15 min of exercise or 1 h after onset of sleep are also shown in Table 1. Patient 9 had a peak GH response to two provocative stimuli of 7.8 μg/L and therefore may have had partial GH deficiency by modern criteria. Patient 18, who had the lowest overnight mean GH concentration, declined further evaluation. Patient 12, who had a peak screening GH value of 3.9 μg/L, had a normal pubertal growth velocity (10 cm/y).

Protocol. All study protocols and consent procedures were approved by the University of Michigan Institutional Review Board. Studies were performed on two consecutive weekends in the Clinical Research Center of the University of Michigan after written informed consent was obtained from a parent and assent obtained from the subject. On each study weekend, boys spent 2 nights in the center. Studies were performed on the second night to allow for acclimatization. On the second day, intravenous cannulae were inserted in each forearm. Lights were turned off at 2200 h, and sleep was monitored by trained nursing personnel.

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Table 1. *Clinical characteristics and study protocol*

Patient	Chronologic age (y)	Bone age* (y)	Wt (kg)	Ht (cm)	Presumed diagnosis†	Pubertal stage‡		Onset of infusion	Dose of testosterone (nmol/h)	Peak provoked GH (μg/L)§
						Pubic hair	Genital			
1	13.9	11	32.3	147	CGD	I	II	2100h	320	31.9[a]
2	13.3	12.5	32.5	146	CGD	II	II	2100h	320	23.7[a]
3	15.5	12.5	39.0	154	CGD	II	II	2100h	320	40.8[a]
4	14.3	12.5	39.7	142	CGD/FSS	II	III	2100h	320	12.4[a]
5	13.4	12	28.8	137	CGD/FSS	I	II	1200h	320	11.9
6	13.2	12.5	30.4	142	CGD	I	II	1200h	320	29.1
7	14.8	12.5	28.7	140	CGD	II	II	1200h	320	18.2[b]
8	15.1	13	68.0	165	CGD	II	II	1200h	320	4.5[a]
9	14.3	13	45.5	145	CGD	I	II	1200h	320	14.0
10	15.4	13	46.6	149	CGD	III	III	1200h	320	7.8
11	17.3	14	44.6	158	CGD	II	III	1200h	320	15.1
12	15.3	14	39.3	155	CGD	III	III	1200h	320	3.9[a]
13	13.0	10	28.4	136	CGD	I	II	1200h	960	25.1[a]
14	13.8	10.5	30.1	141	CGD	II	II	1200h	960	13.2[a]
15	13.9	11.5	39.0	147	CGD	I	II	1200h	960	13.2
16	14.8	11.5	37.0	140	CGD	II	II	1200h	960	13.3
17	13.5	11.5	37.7	146	CGD	II	II	1200h	960	16.1[b]
18	15.5	13.5	49.6	156	CGD	II	II	1200h	960	3.9[a]
19	15.1	13.5	42.6	151	CGD	III	III	1200h	960	19.0
20	15.5	13	56.8	184	FTS	IV	IV	1200h	960	19.1

* By the method of Greulich and Pyle (20).

† CGD, constitutional growth delay; FSS, familial short stature; FTS, familial tall stature.

‡ By the method of Tanner (21).

§ Data followed by *a* represents values 1 h after sleep. Data followed by *b* are values obtained after exercise. All other values are peaks after arginine or insulin administration.

On the first weekend each boy received a 150 mmol saline bolus at a volume matching the T bolus given on the second weekend (10 ml in patients 1–13 and 3 mL in patients 14–20). The bolus was administered at either 2100 h (patient 1–4) or 1200 h (patients 5–20) followed by a 150 mmol saline infusion at 10 mL/h continuing through the end of serial blood sampling at 0800 h the next morning. On the second weekend, T was infused at 10 mL/h. The infusate was prepared as described previously (18) from crystalline T obtained from Sigma Chemical Co. (St. Louis, MO) at a final concentration of 32 μmol/L (patients 1–12) or 96 μmol/L (patients 13–20). All boys received a 320 nmol bolus of T except for patient 13 who received 960 nmol. The bolus was given at 2100 h (patients 1–4) or 1200 h (patients 5–20). T was then infused at 10 ml/h at the doses indicated in Table 1. Blood was obtained from 2000–0800 h every 20 min for GH and every 30 min for T. Estradiol was also determined in three boys (patients 17–19) every 2 h from 2000–0800 h.

Hormone measurements. Serum GH concentrations were measured in duplicate by a modified double antibody RIA as described previously (22). The standard was human pituitary GH obtained from the National Hormone and Pituitary Program. The assay sensitivity was 0.5 μg/L and the intra- and interassay CV were both less than 5%. Serum T and estradiol were determined in duplicate by RIA using kits obtained from Radioassay Systems Laboratories, Inc. (Carson, CA). The T assay sensitivity was 0.35 nmol/L and the intra- and interassay CV were 5 and 8.5%, respectively. The estradiol assay sensitivity was 18 pmol/L and the intra- and interassay CV were 8 and 15%, respectively. SmC was determined commercially through the laboratories of SmithKline Diagnostics Inc. (Sunnyvale, CA). All samples from a subject (saline and T infusion nights) were processed within the same assay.

Statistical analysis. GH pulses, peak amplitude, and total pulse area were determined using the Detect method of Oerter *et al.* (23). The false-positive peak detection level was set at less than 0.1% using the predicted variance model. All values less than assay sensitivity were assigned a value of assay sensitivity. Missing values comprised less than 1% of the total sample and were not replaced. Peak amplitudes were derived by calculating the difference between peak height and the prepeak nadir. Peak area was calculated by the program (area under the curve).

All hormone values were transformed logarithmically. Mean GH values were subjected to one- or two-way analysis of variance for repeated measures for within or between treatment comparisons, respectively. Comparison of GH peak frequency and amplitude between treatments was by Student's paired *t* test. Correlations were made using the Kendall rank correlation coefficient. A *p* level of 0.05 was considered significant. The data are presented as the means ± SE.

RESULTS

Mean serum GH concentrations and GH secretory profiles. Mean GH and T concentrations from 2000 to 0800 h, the number of GH pulses, mean GH pulse amplitude, and total pulse area during saline and T infusion are shown in Table 2. T infusion at 320 nmol/h produced a 2-fold increase in nocturnal T concentration compared to the saline infusion night (patients 1–12), and at 960 nmol/h, produced a 5-fold increase (patients 13–20). Serum estradiol determined in three boys (patients 17–19) who received a 960 nmol/h T infusion, did not increase above the assay detection limit (18 pmol/L) on the T infusion night.

On the saline night, mean GH concentration for all 20 boys was 3.4 ± 0.5 μg/L. Peak frequency was 3.6 ± 0.2 pulses/boy/12 h. In the four boys who received T at 320 nmol/h beginning at 2100 h, the 12 h mean GH concentration was 4.2 ± 1.1 μg/L. Mean pulse amplitude and total pulse area were 10.7 ± 2.4 and 180.2 ± 59.5 μg/L, not significantly different than values

Table 2. *GH concentration and pulse characteristics and T concentration during saline and T infusion*

	Mean testosterone (nmol/L)		Mean GH (μg/L)		Pulses/12 h		Mean pulse amplitude (μg/L)		Total pulse area (μg/L)	
Patient	Saline	T	Saline	T	Saline	T	Saline	T	Saline	T
1	10.1	19.5	4.5	3.8	5	6	10.5	8.7	159.9	126.0
2	0.7	10.9	9.5	7.4	4	4	18.2	17.9	339.1	227.3
3	3.4	5.6	4.7	3.0	3	4	19.2	8.1	170.9	100.7
4	13.0	15.9	1.4	2.6	4	4	5.3	8.0	50.9	78.0
Mean ± SE	6.8 ± 2.9	13.0 ± 3.0*	5.0 ± 1.7	4.2 ± 1.1	4.0 ± 0.4	4.5 ± 0.5	13.3 ± 3.3	10.7 ± 2.4	180.2 ± 59.5	133.0 ± 32.9
5	3.5	11.2	3.2	3.0	5	4	6.9	10.5	107.5	94.4
6	0.6	7.5	1.5	2.3	3	4	6.7	9.2	43.8	76.3
7	0.5	7.5	3.1	4.4	4	3	10.1	17.7	105.6	153.2
8	7.2	10.4	1.9	2.5	4	6	5.3	4.3	76.7	31.5
9	9.7	11.3	2.4	1.4	2	4	10.1	2.8	125.8	118.2
10	5.8	11.1	4.8	4.3	3	3	13.6	8.5	56.8	78.3
11	12.4	15.5	2.2	1.9	5	4	4.2	5.2	82.2	64.8
12	15.3	19.3	2.3	2.1	3	2	6.0	7.7	73.2	63.3
Mean ± SE	6.9 ± 1.9	11.7 ± 1.4†	2.7 ± 0.4	2.7 ± 0.4	3.6 ± 0.4	3.8 ± 0.4	7.8 ± 1.1	8.2 ± 1.6	84.0 ± 9.7	85.0 ± 13.2
13	1.4	28.4	6.2	2.0	3	1	20.9	12.1	223.5	67.7
14	3.8	25.5	1.8	4.1	3	3	6.2	13.6	58.5	140.8
15	2.1	21.1	3.2	2.2	3	5	9.2	4.5	102.4	65.8
16	14.1	37.1	1.0	1.8	4	3	4.6	6.7	35.1	62.5
17	2.3	13.7	4.3	1.9	2	4	19.6	5.7	156.5	64.4
18	0.5	9.1	0.9	0.5	4	4	4.0	2.1	31.0	16.3
19	1.7	13.5	3.5	2.4	5	5	6.7	6.2	126.6	90.5
20	16.9	17.6	5.8	8.4	3	5	20.3	17.1	200.4	278.3
Mean ± SE	4.1 ± 1.9	20.8 ± 3.3‡	3.3 ± 0.7	2.9 ± 0.9	3.4 ± 0.5	3.5 ± 0.5	11.4 ± 2.6	8.5 ± 1.8	116.8 ± 25.9	98.3 ± 28.5

* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$.

obtained during their saline infusion night. Eight additional boys received a T infusion of 320 nmol/h beginning at 1200 h. Mean GH concentration for these boys was 2.7 ± 0.4 μg/L and mean pulse amplitude and total area were 7.8 ± 1.1 and 84.0 ± 9.7 μg/L, respectively. These values were similar to those obtained on their saline infusion night.

Inasmuch as T infusion at 320 nmol/h did not increase GH concentration, eight boys were treated with a T infusion of 960 nmol/h, a dose that approximates that produced by adult men (24). The mean GH concentration (3.3 ± 0.7 μg/L) on the saline night, did not change significantly with T infusion (2.9 ± 0.9 μg/L). Mean GH pulse amplitude and total pulse area were also unchanged. The dynamics of GH secretion with respect to time could conceivably have been altered by T administration. To examine this possibility, GH in the boys who received 960 nmol/h T was analyzed in 3-h time blocks. The 2000–2240 h block represented hours before the onset of sleep. The 2300–0140 h block encompassed the time when most boys fell asleep. As expected, mean GH concentration, pulse amplitude, and area were highest during this time block (Table 3). Although mean GH pulse amplitude and peak area were somewhat lower with T infusion when compared to saline infusion, the differences were not significant. Acute T infusion did not enhance GH secretion.

Somatomedin C and GH. Mean SmC concentration, determined in 17 of the 20 boys, was 103 ± 15 (range 37–276) μg/L. Mean GH pulse area correlated positively with SmC concentration ($z = 2.357$, $p < 0.01$). SmC concentration was also positively correlated with patient wt ($z = 2.033$, $p < 0.05$) and pubertal stage ($z = 2.927$, $p < 0.01$), but not with mean T concentration ($z = 1.286$) or ht ($z = 1.291$). Mean GH concentration and pulse amplitude did not show a significant correlation with ht, wt, pubertal stage, T, or SmC concentration.

DISCUSSION

In our study, we have determined the overnight GH secretory patterns for 20 boys before and during an acute T infusion. Although chronic T treatment increases GH secretion (10, 15) and GH concentration increases with the later stages of pubertal development (4, 5), we did not find an acute effect of T infusion on either mean GH concentration or on the GH secretory pattern. In contrast, we have found that T infusion decreases nocturnal plasma LH concentration within 5–6 h (18), and T infusion at adult male production rates for periods at least as short as 12 h abolishes the nocturnal amplification of plasma LH concentration and LH pulse frequency (19). Thus, although LH secretion can be decreased acutely by infusion of T, GH secretion is relatively resistant to alteration by short-term T infusion even at adult male blood production rates. If it is correct that T in puberty is responsible for increased GH concentration, a time lag between the plasma T rise and an increase in GH secretion may be due to either a time-dependent induction of pituitary synthesis of GH or the time-dependent metabolism of T to other steroids before its effects on the hypothalamic-pituitary axis can be seen.

Stress of hospitalization may have increased GH secretion on the first weekend. If the boys experienced less stress on the second weekend, GH secretion could have been reduced thereby masking a T induced increase in serum GH concentration. The study was deliberately nonrandom in the order of saline or T administration. Saline was always given on the first weekend, because T may have had a lingering effect on hormone secretion 1 wk later. To lessen the impact of the nonrandom study design, acclimatization nights were included on both study weekends. However, further studies, randomizing the saline and T order of

Table 3. *Effect of high dose testosterone infusion on GH concentration and peak amplitude, area, and frequency as function of time*

	Mean GH (μg/L)		Peak frequency (pulses/boy/3 h)		Peak amplitude (μg/L)		Total peak area (μg/L)	
	Saline	T	Saline	T	Saline	T	Saline	T
2000–2400	2.1 ± 0.5	2.5 ± 0.7	0.63 ± 0.26	0.88 ± 0.13	7.4 ± 3.3	7.2 ± 1.6	32.4 ± 18.1	22.6 ± 5.4
2300–0140	6.4 ± 1.4	5.3 ± 1.5	1.25 ± 0.25	1.13 ± 0.13	13.8 ± 3.4	10.7 ± 2.0	62.8 ± 17.7	42.7 ± 11.5
0200–0440	2.8 ± 1.0	3.0 ± 0.9	0.63 ± 0.18	1.00 ± 0.19	10.0 ± 4.1	8.1 ± 1.5	33.4 ± 15.8	23.4 ± 6.4
0500–0800	2.3 ± 1.0	1.1 ± 0.7	0.88 ± 0.23	0.75 ± 0.25	9.7 ± 3.8	5.1 ± 3.7	25.3 ± 10.8	16.0 ± 15.1

administration, will be necessary to prove absolutely that T has no effect acutely, on the GH secretion of pubertal boys.

Serum estradiol levels were determined in three boys during T infusion, and all values were below the level of sensitivity of the assay. Inasmuch as estradiol is known to enhance GH secretion (9, 12), T aromatization to estradiol may be required to produce increased GH secretion in boys. The presumptive role of estradiol in promotion of growth has been recently reviewed (25). Alternatively, increased GH secretion in puberty may be due to a maturational event that is independent of the increase in T but is temporally related to its increase. This seems less likely in view of the recent study of Chalew *et al.* (16) who have shown that in children with constitutional growth delay, GH secretion declines after T administration is stopped, despite the physical maturation of the boys in the study.

The overall mean GH concentration in the boys studied was 3.4 μg/L which is less than reported nighttime mean GH values of 6–7 μg/L in prepubertal healthy children (6, 7). In a study by Bierich (26) nighttime mean GH concentrations for children with constitutional growth delay were in the range of normal control subjects but were 53% of the control group. Bierich (26) suggested that boys with constitutional delay of growth may secrete relatively less GH than their normally maturing agemates. Whether the relative decrease in GH secretion is secondary to a pathologic process occurring in boys with constitutional delay of growth or is a reflection of their pubertal status and/or sex hormone milieu is as yet unknown. Thus it is conceivable that boys with normal GH concentration and normal onset of adolescence might have an altered response to GH to T, unlike our subjects.

Nongonadal anabolic steroids, such as oxandrolone, have also been given to children to enhance their growth velocity. The increase in velocity has not been associated with a change in GH secretion nor with an increase in SmC concentration, in boys with constitutional delay of growth (10). Thus androgens such as oxandrolone, and perhaps T, may exert a primary effect on growth by a direct effect on skeletal tissue rather than by enhancing GH secretion. The increase in serum GH concentration after chronic administration of T may be due to its conversion to estradiol which then may enhance GH secretion.

We did not find a correlation between GH and ht or growth velocity. Albertsson-Wikland and Rosberg (27) found a nonlinear correlation between ht and mean GH concentration for pubertal children ($r = 0.36$) but the correlation was much more striking for the prepubertal children where a linear correlation ($r = 0.69$) was found. A correlation of mean GH and ht was not found in our pubertal subjects, perhaps due to our small sample size or the presence of constitutional growth delay. In our study, GH pulse area, but not mean concentration or pulse amplitude, was positively correlated with SmC concentration. The significance of this observation is unclear but perhaps indicates that the size of a GH pulse is better related to the GH induced rise in SmC than is the mean serum GH content. SmC was also positively associated with pubertal stage in agreement with previous observations (28).

In this study we have found that, in pubertal children with constitutional growth delay, short-term infusion of T does not acutely alter the release of GH by the pituitary nor is there an amplification of GH pulse area. Thus, long-term exposure to T or the secretion of, or conversion to, other pubertal sex steroids such as estradiol may be required to produce the increase in GH pulse amplitude which may be associated with increased growth at puberty. Alternative hypotheses to be explored are that the increased growth velocity observed during T therapy may be related to sex steroid modulation of GH bioactivity or that there may be alterations in GH binding protein which may make more unbound GH available at target tissue GH receptors.

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